Challenges in BCS-based biowaivers

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NIPTE The National Institute for Pharmaceutical Technology & Education

Improving quality and lowering costs of pharmaceuticals

Biopharmaceutics Classification System (BCS)

Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2017
Biopharmaceutics

BCS Class 3: Research path forward

- Quantify excipient interactions with transporters
- Integrate into PBPK models of oral absorption
- Combine with FDA data warehouse of successful BE studies on products with different excipients
- Test via prospective in vivo studies

- Two or more drugs (FDCs)
- Utility of literature data (e.g. how to assess whether data is “good”)

BCS Guidance

- BCS class 1
  - In general, … excipients … in FDA-approved IR solid oral dosage forms will not affect …”
- BCS class 3
  - “Unlike for BCS class 1 products, … BCS class 3 test drug product must contain the same excipients as the reference product. … The composition of the test product must be qualitatively the same … and should be quantitatively very similar to the reference product. Quantitatively very similar includes …”

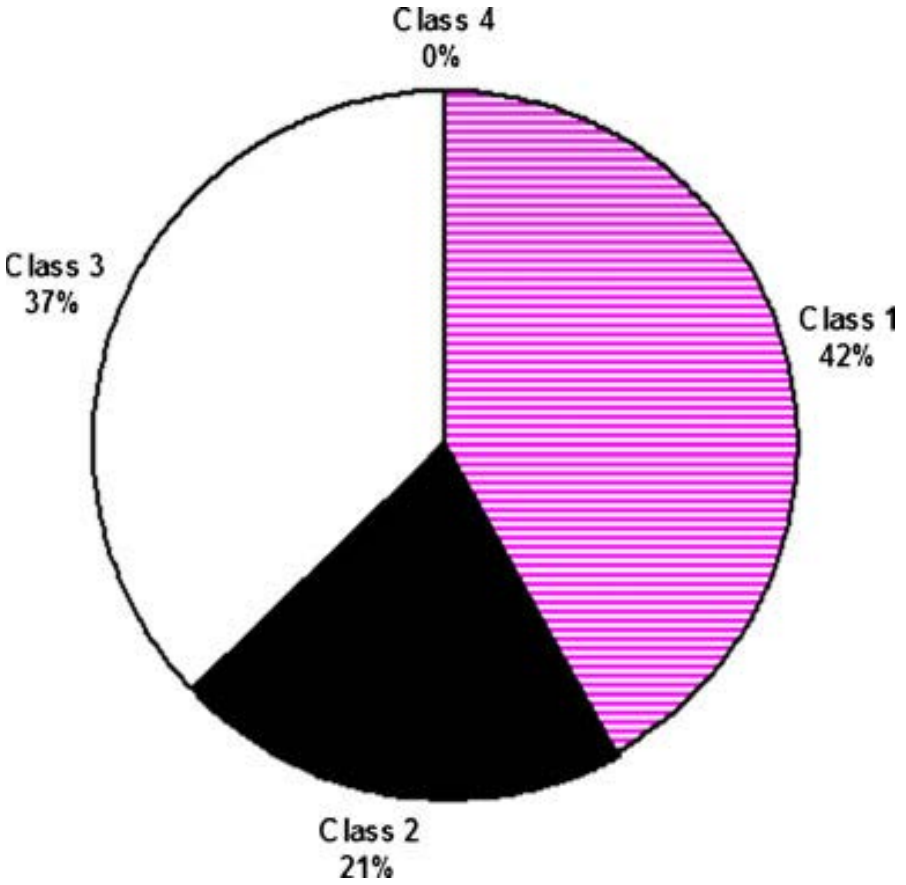
Excipients

Lamictal	Teva lamotrigine
lamotrigine	lamotrigine
lactose	lactose monohydrate
magnesium stearate	magnesium stearate
microcrystalline cellulose	microcrystalline cellulose
povidone	povidone
sodium starch glycolate	sodium starch glycolate
FD&C yellow #6 (100mg), ferric oxide yellow (150mg), and FD&C blue #2 aluminum lake (200mg)	FD&C yellow #6 (100mg), ferric oxide yellow (150mg), and FD&C blue #2 aluminum lake (200mg)
-	colloidal silicon dioxide; pregelatinized starch

Biowaivers and BCS

- Biowaiver – waiver of need to demonstrate in vivo BE based on in vitro BE
- Apply biowaivers to less risky drugs, but which are those?!?
- Biopharmaceutics Classification System (BCS)
  - Based on solubility and intestinal permeability
  - Class 1 = high solubility and high permeability
  - Class 3 = high solubility and low permeability
    - Class 3 biowaivers: Excipients should not modulate drug absorption

BCS class distribution in ANDAs

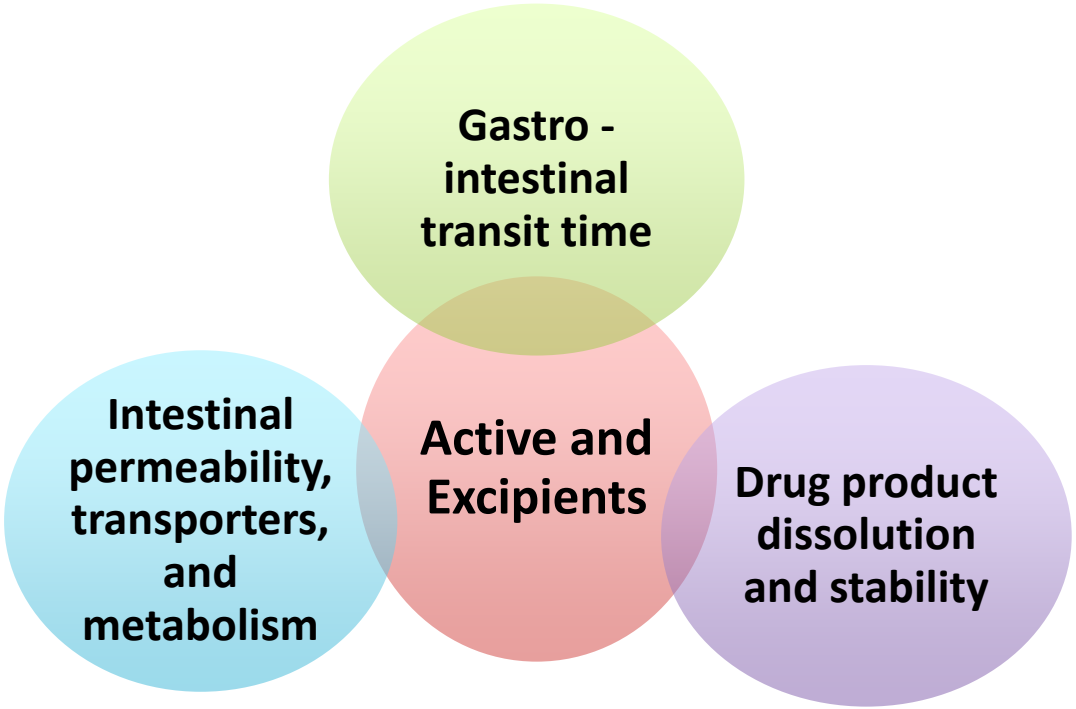


The percent approval of different classes of BCS drugs listed on WHO EML from 2000 to 2011

AK Nair, et al. Statistics on BCS Classification of Generic Drug Products Approved Between 2000 and 2011 in the USA. AAPS J. 14:664-66, 2008.

Excipient Effects

- Class 3 Biowaivers: Excipients should not modulate drug absorption

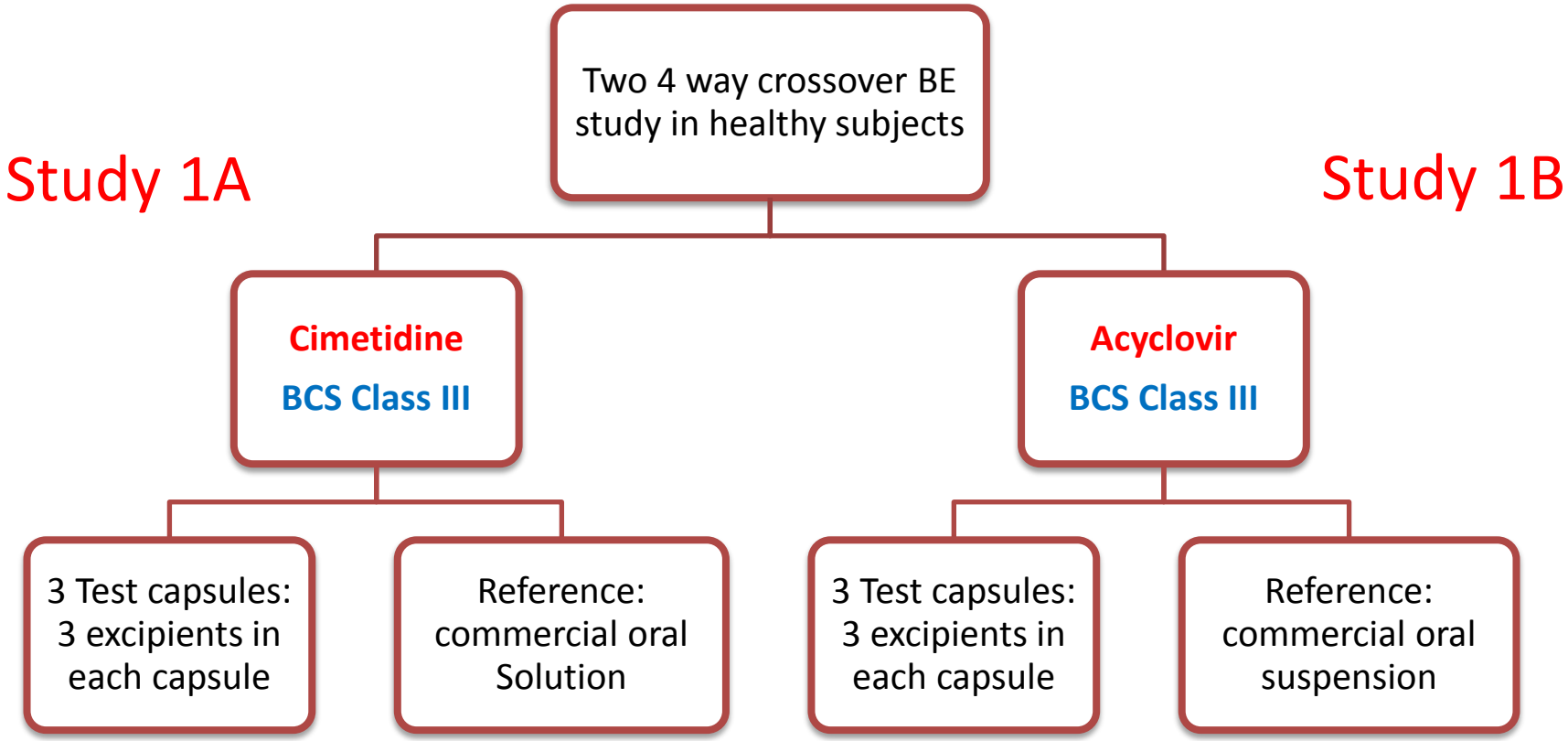


- Vaithianathan, S., et al. (2016): Lack of In Vivo Impact of Common Excipients on the Oral Drug Absorption of Biopharmaceutics Classification System Class 3 Drugs Cimetidine and Acyclovir. DOI: 10.1002/jps.24643. J. Pharm. Sci. 105:996-1005.

Study 1

- Cimetidine and acyclovir – BCS class 3 drugs
- 14 common excipients
- Three capsule formulations for each drug
- In vivo evaluation (2 capsules as single dose)
  - Fasted, single-dose, four-way crossover bioequivalence study (n=24) in healthy human volunteers
- Oral liquid used as reference product
- Average BE analysis to determine impact of excipients

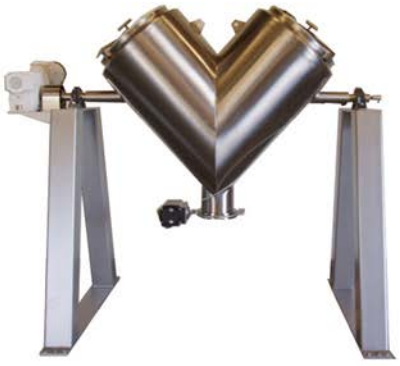
Study 1


Two 4 way crossover BE study in healthy subjects
Study 1A
Study 1B
Cimetidine
BCS Class III
Acyclovir
BCS Class III
3 Test capsules: 3 excipients in each capsule
Reference: commercial oral Solution
3 Test capsules: 3 excipients in each capsule
Reference: commercial oral suspension

Study 2

4 way cross over BE study: Cimetidine

- CimTest-A: < 45mg HPMC
- CimTest-B: < 40mg Mag Stearate
- Commercial Cimetidine oral solution
- Reference Solution: Oral solution without sorbitol



← **V-blender**

Turbula mixer →

Excipient	Recommended maximum allowable amount for a class 3 biowaiver (mg)	Maximum excipient amount studied here (mg)	Typical excipient amount (when present) in an IR tablet or capsule with a total weight of 300mg	Maximum amount (mg) in Inactive Ingredient Database
Microcrystalline Cellulose	Qualitatively same and quantitatively v similar	600	100mg (20%-90%)	1385.3
Hydroxypropyl Methyl Cellulose	Qualitatively same and quantitatively v similar	40	10mg (2%-5%)	444.4
Sodium Lauryl Sulfate	50	50	4.5mg (0.5%-2.5%)	51.69
Corn Starch	900	900	150mg (25%-75%)	1135
Sodium Starch Glycolate	200	200	12mg (4%)	876
Colloidal Silicon Dioxide	40	40	1.5mg (0.1%-1%)	100
Dibasic Calcium Phosphate	600	600	150mg (25%-75%)	635.5
Crospovidone	100	100	10mg (2%-5%)	340
Lactose	900	900	240mg (80%)	1020
Povidone	70	70	7.5mg (0.5%-5%)	240
Stearic Acid	80	80	6mg (1%-3%)	72
Pregelatinized Starch	200	200	150mg (5%-75%)	435.8
Croscarmellose Sodium	120	120	37.5mg (0.5%-25%)	180
Magnesium Stearate	40	40	7.5mg (0.25% to 5%)	400.74

Conclusions and Limitations

- 12 out of 14 were found to be non-problematic: should be no more than quantities studied
- HPMC and microcrystalline cellulose: should be qualitatively the same and quantitatively similar to reference product
- It is possible that other BCS class 3 drugs have properties that differ from cimetidine and acyclovir to render those drugs susceptible to other excipient influences that cause modified drug absorption.
- [T]he greatest concern would appear to be a drug that depends on an uptake transporter that an excipient inhibits by virtue of the excipient having molecular structure similarity to the transporter's pharmacophore or recognition site.

Commentaries

- García-Arieta A., Gordon J., Potthast H. (2016): On The Effects of Common Excipients on the Oral Adsorption of Class 3 Drugs. DOI: 10.1016/j.xphs.2016.01.005. J Pharm. Sci. 105:1353-1354.
  - results obtained by Vaithianathan et al. should not be extrapolated to other drugs
- Vaithianathan, S., et al. (2016): Reply to “On the Effect of Common Excipients on the Oral Absorption of Class 3 Drugs”. DOI: 10.1016/j.xphs.2016.02.028. J. Pharm. Sci. 105:1355-1357.

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